SMOKING *and* HEALTH

REPORT OF THE ADVISORY COMMITTEE
TO THE SURGEON GENERAL
OF THE PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

Chapter 11

Cardiovascular Diseases

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Chapter 11

INTRODUCTION

It has been suggested repeatedly that smoking may have adverse effects on the cardiovascular system. Recently, studies of large groups of people have shown that cigarette smokers in particular are more prone to die early of certain cardiovascular disorders than non-smokers. Chief among these disorders is coronary artery disease, and the present chapter deals mostly with this subject. The chapter begins with a summary of information about the acute effects of smoking on the cardiovascular system. This is followed by a brief account of coronary disease, its frequency in different kinds of people, and the many factors known or thought to affect the likelihood of its development. The aim here is not to review critically our knowledge of coronary disease but only to give background for what follows. Next is summarized the information currently available from study of large population groups on the association of cigarette smoking with an increased tendency to have coronary disease. There follows a brief discussion of smoking and non-coronary cardiovascular disease. Finally, there is a short review of evidence relating to the question of whether cigarette smokers may, as a group, differ from non-smokers in ways not caused by smoking itself. Mortality ratios showing the association between cigarette smoking and deaths from cardiovascular disease, especially coronary disease, do not indicate the magnitude of the burden. This can be better appreciated from consideration of the following facts: cardiovascular disease deaths now total more than 700,000 annually in the United States. Of these more than 660,000 were due to heart disease, with more than 560,000 due to arteriosclerotic heart disease including coronary disease. The remaining approximately 40,000 were ascribed to disease of other parts of the cardiovascular system. Deaths from lung cancer total approximately 30,000. A mortality ratio of 1.7 for coronary heart disease among cigarette smokers in the seven prospective studies represents from 32.9 percent to 51.7 percent of all excess deaths, whereas the much higher lung cancer mortality ratio of 10.8 from the same studies represents only 13.5 percent to 21.0 percent of total excess deaths (Chapter 8, Tables 19, 25).

PERTINENT PHARMACOLOGY

The acute cardiovascular effects of smoking in man and experimental animals are like those caused by nicotine alone. A smoker who inhales gets usually 1–2 mg of nicotine from a cigarette (56, 57).

Low concentrations of nicotine stimulate sympathetic ganglia, and high concentrations paralyze them. Parasympathetic ganglia respond in the same way but are less sensitive. Nicotine can also have a sympathomimetic effect by causing the discharge of norepinephrine and epinephrine from chromaffin cells in various tissues, including heart, vessels, and skin (9, 10, 11). In addition, nicotine produces effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. When nicotine is given intravenously in increasing doses to dogs or cats the first effects, at about 1 microgram/kg body weight, are increased breathing and sympathetic stimulation, with predominant vasoconstriction, cardiac acceleration, and rise in blood pressure, resulting from stimulation of the aortic and carotid bodies (17). Doses of 4 to 8 micrograms/kg can stimulate pulmonary and coronary chemoreflexes which produce opposite effects. If all these receptors are inactivated, much higher doses are needed to evoke the cardiovascular effects of sympathetic stimulation, presumably through action on sympathetic ganglia or chromaffin tissue. Intravenous administration of nicotine in the experimental animal causes a discharge of epinephrine from the adrenal medulla, and in man heavy cigarette smoking produces an increased urinary excretion of catecholamines (84, 99).

Smoking 1–2 cigarettes causes in most persons, both smokers and non-smokers, an increase in resting heart rate of 15–25 beats per minute, a rise in blood pressure of 10–20 mmHg systolic and 5–15 mmHg diastolic (76, 78, 85, 86), and an increase in cardiac output of about 0.5 l/min/sq.m (75). There is a decrease in digital blood flow and a consequent drop in finger and toe temperature (31, 78, 103). The decrease in peripheral blood flow which normally follows smoking does not occur in a sympathectomized limb, indicating that the effect is mediated primarily by the sympathetic nervous system rather than through the release of catecholamines from other sites or the direct effect of nicotine upon the smooth muscle of the blood vessels themselves (103). Intravenous nicotine, and probably cigarette smoking as well, can produce a slight transitory increase in the blood flow to resting calf muscle (79).

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This section on pharmacology of nicotine is so brief that it does not do justice to the considerable amount of information available in 1964. The opening paragraph cites (57) Larson, Haig and Silvette (1961) which is the most extensive monograph on Tobacco. The cardiovascular effects of nicotine are discussed in pages 14 to 232, and the relation of tobacco to cardiovascular disease in pages 653 to 686. However, the monograph is mentioned only in reference to the amount of nicotine absorbed.

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In the dog, nicotine and cigarette smoke cause an increase in coronary flow as the blood pressure, cardiac output, and heart work increase (30, 53). These effects resemble those of epinephrine. Nicotine has been found to cause a transient decrease in cardiac oxygen utilization followed by a slight increase (53). Relatively little information is available about the effect of smoking on coronary blood flow in man. In normal subjects it is reported that cigarette smoking produces an early increase in coronary flow as heart work increases, but there is little change in oxygen utilization by the myocardium (2). With continued "steady state" smoking the coronary flow and cardiac oxygen utilization are maintained at the resting level in both normal subjects and persons with coronary heart disease, despite increased blood pressure, heart rate, and heart work (74). A larger experience must be gathered in this field before statements about the acute effects of smoking on the human coronary circulation can be made with assurance. The atherosclerotic rabbit heart, like the normal rabbit heart, shows an initial drop in coronary flow on administration of nicotine, but demonstrates less of a subsequent increase above the resting level than does the normal heart (97). These effects are said to be equivalent to those produced by norepinephrine in doses one-tenth as large as the nicotine dose.

Little or no change in the electrocardiogram of most normal persons or cardiac patients, except for an increase in rate, is produced by smoking or by the intravenous injection of an equivalent dose of nicotine (82, 93). In some persons there is a slight depression of the S–T segment and a flattening of 1–2 mm in the T wave of the limb leads. These changes are not like those associated with myocardial ischemia. Rarely in persons with true angina, an attack of pain is precipitated by smoking. An ill-defined syndrome consisting of chest pain, palpitation, and shortness of breath, known as "tobacco angina", has been described as occurring in smokers who do not have organic heart disease, but it is rarely diagnosed today (73, 82). Extrasystoles and other cardiac arrhythmias have been reported to be caused by smoking, but such cases appear to be unusual.

The ballistocardiogram obtained from a high-frequency table is sometimes changed by smoking a cigarette from a normal pattern to one said to be typical of coronary disease (78, 91). This phenomenon is rare in healthy persons below 50, becomes increasingly common with advancing years in apparently healthy persons, but is particularly prone to occur at any age in persons with actual coronary disease. The effect has been used as a "stress test" to help uncover coronary disease, but false positive and negative results are common. The ballistocardiographic changes on smoking have been variously interpreted as resulting from impaired myocardial contractility (78), from changes in the peripheral circulation (82), or from uncertain causes related to the physical properties of the high-frequency table as well as changes in the circulation.

Cigarette smoking causes an increase in the concentration of serum-free fatty acids in man (59), apparently mediated by stimulation of the sympathetic nervous system (51). Although continued administration of epinephrine to dogs over many hours can produce substantial increases in serum cholesterol, phospholipids, and triglycerides, such an effect has not yet been reported from nicotine or tobacco smoke (48, 92).

The clotting time of the blood can be decreased 50 percent or more in experimental animals by stimulation of the sympathetic nervous system or by administration of epinephrine (12, 13, 14), but attempts to demonstrate that cigarette smoking alters the clotting properties of the blood in man have been unsuccessful (5, 63). A decrease in platelet survival *in vivo* has been found after smoking (63). Cigarette smokers have been reported to show substantial decreases in hematocrit, hemoglobin, and platelet counts after abstinence of 1–2 weeks (25), but hemoglobin concentrations are alike in smokers and non-smokers of the same population group (64).

Attempts have been made to induce atherosclerosis in rats by the chronic administration of nicotine for periods up to a year without success (93).

Tobacco has antigenic properties (29, 43). Rats can be sensitized to tobacco extracts by intraperitoneal injection. Over a third of smokers demonstrate a positive "immediate" skin reaction to such extracts while only about 10% of non-smokers are said to give positive tests. The presence of serum reagins in persons with positive skin tests has been demonstrated by passive transfer techniques. Persons with thromboangiitis obliterans and smokers with occlusive vascular disease of other types are said to show a much higher incidence of positive skin tests than healthy smokers. The cardiovascular diseases which have been related to smoking, however, do not in general resemble those usually ascribed to an immune mechanism.

In man and experimental animals smoking or the injection of nicotine causes increased secretion of antidiuretic hormone. The renal effects of this are easily demonstrable but the quantity of hormone secreted in response to smoking is probably too small to have significant vascular effects (17).

In summary, the acute cardiovascular effects of smoking and of nicotine closely resemble those of sympathetic stimulation, and to a considerable extent are mediated by excitation of the sympathetic nervous system. No additional or unique cardiovascular effects have been demonstrated which, in the light of our present understanding, seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease.

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The information on the effect of smoking on coronary blood flow in man was sufficient to show that there was no harmful influence. The conclusions of (2) Bargeron et al., 1957 and (74) Regan et al., 1961 were similar to those obtained by six groups of investigators administering nicotine in dogs (see page 270). At the time Bargerson et al. and Regan et al. 1961 completed their experiments, their conclusions were accepted because the nitrous oxide technique was the only means of measuring coronary blood flow and myocardial metabolism in man. The observations by Regan et al 1961 have not been disproven by subsequent reports. The Discussion quoted from the article is as follows:

Discussion

The experimental conditions of this stu were limited to evaluation of the sustain effects of cigarette smoking upon the m cardium of man after the peripheral he dynamic changes had become well establish Consequently, interpretation of the data ca not be applied without reservation to t acute changes occurring immediately af the onset of smoking, which may well be qualitatively different.[6] If one assumes, however, that nicotine is the principal pharmacologic agent in tobacco smoke, then the effects of intracoronary infusion of this substance are of some interest. In the intact dog it has not been found to modify coronary blood flow when injected into the anterior descending artery, despite substantial increase in myocardial contractility.[9] Left coronary perfusion with nicotine also has failed to increase flow in the atherosclerotic rabbit heart, despite cardiac acceleration and enhanced contractility.[10] These studies, in which different methods of determining coronary flow have been employed, tend to reduce the possibility that these results in man represent an artifact of the nitrous oxide method.

Augmentation of coronary blood flow may usually be anticipated when there is an increase in heart rate, systemic arterial pressure, cardiac output, and left ventricular work. In this manner, the apparently greater oxygen requirement of the myocardium would be severed. Failure to find such increases of myocardial blood flow and oxygen consumption in the coronary subjects during cigarette smoking may plausibly be related to the "fixed coronary resistance" alleged to exist in such patients.[11] That the abnormal coronary vasculature is not responsible becomes apparent from the similar response in the subjects without evidence of coronary disease. In view of the evidence that ventricular contraction acts to impede coronary flow within the left ventricular wall,[12] the enhanced ventricular contractility as reflected by left heart work may have produced such an effect. This view is difficult to accept, since the failure of coronary flow to meet the need for greater oxygen usage should be associated with augmented oxygen extraction.

Although many of the effects of smoking and nicotine infusion mimic those of catecholamine administration,[5] an evaluation of endogenous catechols in plasma in response to smoking too small to affect the coronary vasculature appears unlikely. On the contrary, small graded doses of catecholamine induce changes in coronary flow before increments in rate and pressure.[13] Another humoral agent possibly released during smoking is antidiuretic hormone.[5] Its potent coronary vasoconstrictor properties raise the possibility that any undesirable effects of smoking could be effected through its activity. Even though the plasma levels of vasopressin probably are not sufficient significantly to restrict coronary blood flow per se, the lack of increased flow despite increments of rate and pressure may represent a restrictive effect of low hormone concentration upon the response to these stimuli of coronary vasodilatation.

It would appear that an enhanced ratio of left ventricular work to oxygen uptake may be maintained for some time without cardiac dysfunction. Such is the case in animals with chronic complete heart block[14] or in those subjected to expansion of intravascular volume.[15] Such disproportion in coronary subjects, however, if large enough, could presumably produce ischemia symptoms. This circumstance, as suggested by this study, would appear to be an uncommon occurrence.[16]

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Tobacco angina. In 1963, Oram and Sowton reviewed the literature and his experiences on tobacco angina. Although the condition is rare, its occurrence has been ignored in prospective and clinical studies of angina pectoris. The subject is discussed in pages 15 to 18. Since the article does not appear in the 1964 or subsequent reports, the summary is reproduced below:

Summary

The term tobacco angina as previously used has become meaningless, and covers at least five separate syndromes to which we have drawn attention. A definition of tobacco angina is offered.

Angina as a result of smoking is a real entity, but rare. Including our three patients, only 17 convincing examples, confirmed electrocardiographically, have been recorded. The commonest type occurs in patients who already have typical Heberden's angina due to coronary disease and precipitated by the more usual causes. A very rare type is that occurring in apparently healthy young people in whom electrocardiographic changes characteristic of coronary insufficiency appear within a few seconds of smoking a cigarette, accompanied or unaccompanied by cardiac pain, but in whom the electrocardiographic changes and pain are said not to be induced by other causes such as exertion, emotion, and cold. We feel it is likely that follow-up studies of these rare patients might later reveal coronary disease.

It is important when searching for patients suffering from tobacco angina to investigate them not only while they are smoking, but after smoking followed by exercise, and after exercise followed by smoking, otherwise examples will be missed. Of 309 smokers with angina questioned concerning the possible role of cigarette smoking in causing cardiac pain, 20 claimed to have angina on smoking. These were re-examined clinically, and electrocardiograms were taken at rest, after smoking, after smoking followed by exercise, and after exercise followed by smoking. Only two examples of genuine tobacco angina were found by this means.

Our three patients had ischaemic heart disease with chest pain, and electrocardiographic evidence of coronary insufficiency was produced by exercise and by smoking cigarettes or cigars. No significant change in blood-pressure accompanied the cardiac pain and electrocardiographic changes which resulted from smoking. These effects induced by smoking were invariably accompanied by tachycardia, but were not secondary to tachycardia as induced by intravenous atropine.

Neither smoking herbal cigarettes nor the intravenous injection of normal saline induced angina or electrocardiographic changes.

The most satisfactory explanation of the cardiac pain and electrocardiographic changes appears to be that nicotine gives rise to coronary insufficiency not by coronary vasoconstriction as previously supposed but by coronary vasodilatation. In spite of this vasodilatation the blood supply to the myocardium becomes insufficient because of the concomitant increase in cardiac work, resulting from an increased cardiac rate, rise in blood-pressure, or both. Possibly also the liberation of catechol amines has a deleterious effect on the metabolism of the myocardium.

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The vasodilatation results from liberation of catechol amines from stores in or near the blood-vessel walls, including the chromaffin tissue along the coronary vessels themselves. Catechol amines cannot be liberated as a result of stimulation of sympathetic ganglia by nicotine, as the blood level of nicotine attained by smoking is too low for this purpose. It is, however, sufficient to liberate catechol amines from blood-vessel walls.

The explanation of the rarity of tobacco angina is not clear. Presumably a few individuals are in some way hypersensitive. The investigation of skin sensitivity to tobacco should be made by using fractionated extracts of tobacco smoke rather than extracts of tobacco itself. We have been unable to demonstrate any sensitivity to either.

To test the theory that release of catechol amines by nicotine leads to tobacco angina, we tried six drugs which might be expected to block the nicotine effect, and four which might be expected to aggravate it. The former group consisted of dihydroergotamine, antiserotonin, reserpine, hydrocortisone, guanethidine, and methyl dopa, while the latter comprised serotonin and three monoamine oxidase inhibitors. The results are given in detail. Surprisingly, the monoamine oxidase inhibitors had a protective effect in all three patients. None of these drugs blocked the effect of exercise.

Our results support the belief, previously based on animal experiments, that nicotine exerts an action like that of the sympathetic stimulants because it liberates noradrenaline.

If it is thought by the patient that his angina is induced more easily during the time he is smoking, he should be persuaded to abstain for one month, and the electrocardiogram should then be repeated. If clinical improvement is reported and the height of the T wave has also improved, he should be permanently discouraged from smoking.

Indiscriminate advice against smoking, as far as angina is concerned, is not justified, and each patient needs individual assessment.

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GENERAL OBSERVATIONS ON CORONARY HEART DISEASE

Heart disease is the most common cause of death in our population, and coronary disease is the commonest variety of fatal heart disease (59). In 1961 there were 1,701,722 deaths from all causes in the United States. Heart disease deaths numbered 663,391 of which 502,351 were due to arteriosclerotic heart disease.

The disorder consists of obstruction or narrowing of the coronary arteries, reducing the blood supply to the heart muscle. The underlying cause of the obstruction is coronary atherosclerosis, but an acute coronary artery occlusion is often caused by the formation of a blood clot in a diseased artery. The common manifestations of coronary disease are angina pectoris, recurrent brief attacks of chest pain caused by inadequate blood supply to the heart muscle; myocardial infarction, or necrosis of a portion of the heart muscle due to acute loss of blood supply; congestive heart failure, a chronic state caused by inability of the heart to pump enough blood to satisfy the demands of the body; and sudden death resulting from cardiac standstill or ventricular fibrillation.

There are considerable differences in the prevalence of coronary heart disease in different countries, and often in different ethnic and socio-economic groups within a particular country (49, 62). The reported death rate of arteriosclerotic heart disease, which is primarily coronary disease, is higher in the United States than in other countries. It is also quite high in New Zealand, Australia, South Africa, Canada, and Finland, and moderately high in Great Britain. The death rate in Norway, Sweden, and Denmark is roughly half that in the high death rate countries (65). The death rate in Japan appears to be about one-sixth that in the United States, although persons of Japanese origin living in the United States are said to have a death rate similar to that of the general population of this country (52).

Because of changing diagnostic skills and revisions in nomenclature of disease, it is difficult to be certain of the change in incidence of coronary disease in the United States over the past few decades, but there is a general opinion that the incidence is increasing in this country and in England, particularly in the younger male group (59, 62, 65, 83). In 1955 the mortality rate from arteriosclerotic heart disease was reported to be about 240 per 100,000. Although this is an increase of more than 50% over the rate in 1940, it has been estimated that less than 15% of the increase represented a real change in incidence of the disease, the remainder depending upon changes in diagnosis, in nomenclature and in the age of the population (59). Since 1955 the death rate from coronary disease (ISC 420) and from arteriosclerotic and degenerative heart disease (ISC 420 and 422) has continued to increase gradually. In 1960 the age-adjusted death rate from 420 and 422 was 336 per 100,000 for white males and 160 for white females (55).

Although the basic cause or causes of coronary heart disease are obscure, certain factors other than smoking are known or thought to predispose to the condition or to be associated with an increased incidence.

The incidence of coronary heart disease in men under 45 is about 5 times as great as that in women (Table 1) (15, 20, 59, 62). In both sexes the incidence increases with advancing years. After the menopause the incidence increases rapidly in women, and at age 80 the death rates from coronary disease are about the same for the two sexes. Coronary thrombosis plays a relatively more important role in precipitating myocardial infarction in young men than it does in old men (105). In studies of large population groups coronary disease has been associated with elevation of the serum cholesterol, hypertension, and marked overweight (19, 20, 24, 36, 45, 59, 62).

Some individual characteristics have been said to be associated with coronary disease. There is a significant familial tendency to develop it (36, 69, 81, 96). Persons with a mesomorphic constitution are said to be more vulnerable than endomorphs and ectomorphs (59, 62, 83). A coronary-prone personality has been described as the aggressive, competitive person who takes on too many jobs, fights deadlines, and is obsessed by the lack of adequate time for the performance of his work (33, 34, 35).

TABLE 1.—*Death rates per 100,000 from arteriosclerotic and degenerative heart disease* by sex and age, United States, 1958–60*

Age Group	Males	Females	Both Sexes
Under 35	3.3	1.2	2.2
35–44	90.2	18.3	53.3
45–54	353.7	79.8	213.5
55–64	928.5	314.5	610.2
65–74	2129.2	1062.0	1569.5
75 or over	4765.1	3738.4	4179.7

*Includes ISC numbers 420 and 422.

Source: WHO Epidemiological and Vital Statistics Report, Vol. 16, No. 2, 1963 (15).

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Some of the articles cited in this page discuss the interrelationship between smoking and other risk factors. One example is (81) Russek and Zohman, who described hereditary predisposition as well as other risk factors in coronary heart disease of young adults. Although smoking was prevalent in the coronary group, it appeared to the authors to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease.

TOBACCO. Prior to the attack, 90% of the coronary patients indulged regularly in the use of tobacco, while 10% were either nonsmokers or participated on rare occasions. Among controls, on the other hand, 62% were habituated while 38% smoked occasionally or not at all. Heavy smokers were also found to be far more frequent in the coronary group. Thus, 70% of their number had smoked at least 30 cigarets per day prior to their attack as compared with only 35% in the contratest group. These observations indicate, therefore, that smoking was not only more prevalent in the coronary group but also that the coronary patients who had smoked were more heavily addicted to the use of tobacco. Nevertheless, it is not clear from these findings whether nicotine is a predisposing factor in coronary heart disease or whether its more frequent and excessive use among young candidates is merely a reflection of the heightened emotional tension so prevalent among them.

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Certain occupations have been said particularly to favor the development of coronary disease, notably those which feature responsibility and stress (34, 81, 87), and which are sedentary in nature (71). Others (33, 72, 90) have not found that executives are more prone to coronary disease than non-executive personnel. Physicians have been said to have 3 or 4 times as much coronary disease as farmers or laborers (87), and general practitioners to have 3 times as much as dermatologists (81). Occupations involving much physical activity are said to be protective (65, 67, 77). City life has been said to be more closely associated with coronary disease than suburban life, and men who drove more than 12,000 miles a year seemed, in one study, more prone to the disease than those who drove less (64).

It has been widely held, and occasionally denied, that a diet high in saturated fat predisposes to the development of coronary disease (40, 52, 69, 81). A correlation between the national incidence of coronary disease and the percentage of food calories available as saturated fat has been reported among those countries for which adequate data exist (66). The serum cholesterol tends to rise when saturated fat is added to the diet, and it falls significantly when unsaturated fat is substituted (106). It has also been suggested that general over-nutrition, rather than excess saturated fat predisposes to coronary disease, on the grounds that the correlation of coronary disease with total available calories or sugar consumption per capita is as good as that for percentage of calories in fat (106).

In general, it is apparent that multiple personal and environmental factors can markedly affect the incidence of coronary disease.

SMOKING AND CORONARY HEART DISEASE

Over the last two decades a considerable number of epidemiologic studies on different populations, employing different techniques, have shown with remarkable consistency a significant relationship between cigarette smoking and an increased death rate from coronary heart disease in males, particularly during middle life. There has been little dissenting evidence. The association of coronary disease with the use of tobacco in other forms has not been striking. The documentation for these statements is given in the following paragraphs. Particularly important is the information in Chapter 8, Mortality.

English et al. (70) found the incidence of coronary disease in male patients at the Mayo Clinic about 3 times greater in cigarette smokers than in non-smokers in the 40–59 year age range, but found little relation to smoking above (or). Russek (61) reported a similar relationship, but less striking, in young men with coronary disease. Mills (64) in a study of reported mortality in a Cincinnati population found that heavy smokers in the 30–59 year age range had twice as high a death rate from coronary disease as non-smokers. Male Seventh Day Adventists, who are non-smokers, were found by Wynder and Lemon (104) in a study based on hospital admissions to have significantly less coronary disease and to develop it later in life than the general male hospital population. Haag and Hammer (37) reported that employees in the tobacco industry, who tend to smoke heavily, had a lower death rate for cardiovascular disease than the general population in their geographic region, but no report was made of mortality rates within the tobacco-worker group, divided by smoking habits. The study has been criticized on this and other grounds (16).

Large-scale prospective studies of mortality in British physicians (Doll and Hill, 21), United States males 50–69 recruited by volunteer workers (Hammond and Horn, 38, 39, 40, 42) and V.A. Life Insurance policyholders (Dorn, 22) have confirmed the association of death from coronary disease with cigarette smoking. In the British study, a step-wise association was found between the amount of tobacco consumed (not entirely cigarettes) and the mortality from coronary disease. The association occurred in the 35–54 year age range, but not in older men. Hammond and Horn found a similar graded relation-ship between coronary deaths and cigarette smoking, the death rate being more than twice as great in men who smoked over a pack a day as in non-smokers. Men who had stopped smoking for more than a year at the start of the study had a coronary death rate lower than those who continued.

Studies on special groups of men, such as longshoremen (Buechley et al. 8) members of a fraternal order (Spain and Nathan, 83) and industrial employees (Paul et al. 71) which, in the latter two instances, incorporated clinical coronary disease, as well as coronary deaths, also have shown a relation-ship between coronary disease and smoking. The relationship was closer for men under 55 than for older men, and closer for myocardial infarcts and death than for angina pectoris (70, 83).

The long-term prospective studies of cardiovascular disease in Framingham (19) and in Albany (23) which have features a painstaking search at regular intervals for clinical manifestations of disease, have, on pooling the data (Doyle et al. 23) shown a three-fold increase in the incidence of myocardial infarction and coronary deaths in men who are heavy cigarette smokers as compared to non smokers, pipe and cigar smokers, and former cigarette smokers. In the pooled data the incidence of angina pectoris did not show a significant association with cigarette smoking. The lack of this particular relationship had been suggested on the basis of clinical experience (White and Sharber, 102).

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